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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

NOV 22 1994

MEMORANDUM

Subject: Data Waiver for Additional Testing on the Metabolic 1/2 Life of Difethialone

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

P.C. Code 128967
Barcode D208090
Submission S474729
MRID 420650-09
MRID 420650-10

From: Ray Landolt 11/21/94
Review Section I
Toxicology Branch II
Health Effects Division (7509C)

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Thru: Mike Ioannou, Section Head
Review Section I
Toxicology Branch II
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and
Marcia van Gemert, Branch Chief
Toxicology Branch II
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M. Ioannou 11/21/94

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Registrant: LiphaTech, letter of March 28 1994

Action Requested: The registrant has cited two previously submitted modified metabolism studies with a data waiver request from additional testing to demonstrate the 1/2 life of difethialone.

Recommendation: 1. The data waiver request from additional testing to demonstrate the 1/2 life of difethialone is granted.

2. Data requirements for nonfood uses of difethialone are complete. These requirements are consistent with FIFRA 88 data requirements for reregistration of anticoagulant rodenticides.

Conclusion: Two previously submitted modified metabolism studies (MRID 420650-09 and 420650-10) have been reviewed. These two studies are acceptable and satisfy the data request to demonstrate the 1/2 life of difethialone.

Difethialone is rapidly absorbed from the GI tract with blood levels detected within 1/2 hour. Tissue residues were highest in the liver with an estimated 1/2 life of 126 days from a single oral dose at 0.5 mg/kg and 80 days from repeated oral doses at 0.06 mg/kg. Elimination was slower in males than in females.

Consideration Given this Request: Toxicology Review of February 5, 1990 requested a modified metabolism study to demonstrate the 1/2 life of difethialone. Subsequently, the toxicity data submitted on difethialone were subjected to New Chemical Screening Review. Toxicology Review of March 17, 1992 determined that two metabolism studies in rats (MRID 420650-09 and 420650-10) did not pass the New Chemical Screen. These studies did not meet the acceptance criteria for review due to too few animals used for determination of plasma, tissue and excreta radioactivity. In response to this data waiver request these studies have been reviewed (attached) and satisfy the data request for a modified metabolism study.

A data waiver was granted for a General Metabolism Study (85-1) with Toxicology Review of June 2, 1992.

Toxicology Profile for Technical Difethialone

Difethialone is an anticoagulant rodenticide with proposed terrestrial and residential nonfood uses. The following data requirements for a "New Chemical" are consistent with FIFRA 88 data requirements for reregistration of anticoagulant rodenticides. The remaining 158.340 Toxicity Data Requirements (ie, chronic) have either been waived or are not required for the registration of these rodenticides.

Toxicology Data Requirements for Technical Difethialone

Acute Testing:	MRID No.	DER	Satisified
81-1 Acute Oral Toxicity	402689-03 426877-04	006460 010732	Yes
81-2 Acute Dermal Toxicity	402689-06 426877-06	006460 010732	Yes
81-3 Acute Inhalation Toxicity	402689-07 426877-07	006460 010018	Yes
81-4 Primary Eye Irritation	426281-06	010732	Yes
81-5 Primary Dermal Irritation	402689-09	006460 010732	Yes
81-6 Dermal Sensitization	426877-01	010732	Yes
Subchronic Testing:			
82-1 90-Day Oral Toxicity	407914-02 426877-10	007523 010732	Yes
Chronic Testing:			
83-3 Developmental-Rat	433038-01 422038-02	010732	Yes
Mutagenicity Testing:			
84-2a Gene Mutation	420650-08	010732	Yes
84-2b Chromosomal Aberration	4260650-07	010732	Yes
84-4 Other Genotoxic Effects	-	-	No*
Special Testing:			
85-1 Metabolism, modified **	420650-09 420650-10	This Review	Yes
86-1 Antidotal Treatment-Rat	420650-13	010732	Yes
Antidotal Treatment-Dog	421143-01	010732	Yes

* Waived for difethialone and other anticoagulant rodenticides.
** A data waiver for a General Metabolism Study (85-1) was granted. The data request for a modified metabolism study is satisfied.

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Primary Review by Ray Landolt 11/17/94
Review Section I, TBII/HED (7509C)
Secondary Review by Mike Ioannou JMI 11/17/94
Review section I, TBII/HED (7509C)

DATA EVALUATION REPORT

Study Type: Metabolism, Modified to Determine 1/2 Life from Repeated Oral Doses

Test Material: Difethialone (LM 2219)

Classification: Anticoagulant Rodenticide

P.C. Code 128967
Barcode D208090
Submission S474729
MRID 420650-09

Study No.: L-AV/VN

Date of Study: March 23, 1991

Title of Report: Compared Hepatic Kinetics of Brodifacoum and Difethialone in the Rat, After Oral Administration of 0.06 mg/kg Once Weekly for 4 Consecutive Weeks

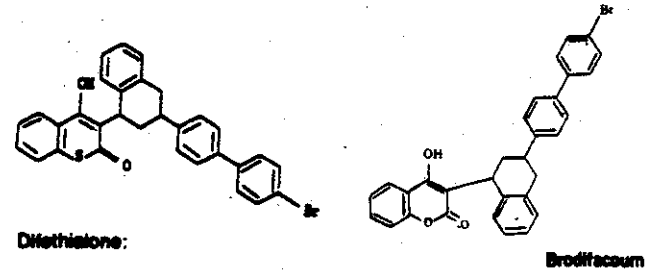
Author: M. Belleville

Testing Facility: Lyonnaise Industrielle Pharmaceutique, France

Sponsor: LiphaTech, Inc.

Executive Summary: To compare the pharmacokinetics of two structurally related anticoagulant rodenticides, oral doses of 0.06 mg/kg were administered of either difethialone or brodifacoum to 9 groups of 5 male Wistar rats/group in four consecutive weekly doses. The test groups were sacrificed at nine successive intervals starting with 24 hours after the last dose, then at 2, 4, 6, 8, and 10 weeks followed by 4, 5, and 6 months (MRID 420650-09).

Hepatic residue levels of brodifacoum were elininated slower than difethialone with a calculated 1/2 life of 140 and 80 days, respectively. After 6 months the hepatic concentrations of brodifacoum and difethialone were 21 and 7% of the total dose (68 ug/kg) administered.



Difethialone: Brodifacoum

This study does not satisfy the Guideline Data Requirement for a General Metabolism Study (85-1), but is acceptable and does satisfy the data request for a modified metabolism study to demonstrate the 1/2 life of difethialone.

A. Materials

1. Difethialone, bromo-4'-biphenyl-4-yl-3-tetrahydro-1-2-3-4-naphthyl-1,3-hydroxy-4-2H-1-benzothiopyran-2-one of lot PS 736 and a purity of 99.15% was used in this study.

   Brodifacoum,3-[3-(4'-bromo-[1,1'-biphenyl]-4-yl)-1-2-3-4-tetrahydro-1-naphthalenyl]-4-hydroxy-2H-benzopyran-2-one of lot JCC 4264 and a purity of 100% was used in this study.

   Stock solutions were prepared with the respective test materials at 12 mg/ml in polyethyleneglycol 300. These solutions were further diluted to 0.012 mg/ml in 0.5% aqueous methylcellulose to administer a constant volume of 5 ml/kg.

2. Ninety-five Wistar male rats (from IFFA-CREDO Center, France) weighing 215.4 + 3.7g were housed 5 animals/cage with food and water available ad libitum. Animals were not fasted.

B. Methods

1. Animals were allocated to two groups of 45 rats/group. One group to receive difethialone, the other brodifacoum with 5 rats in a vehicle control group. Each of the test groups were divided into 9 groups of 5 rats/group. Each test group received 4 single oral doses at weekly intervals for four consective weeks at 0.06 mg/kg. The dose administered (0.06 mg/kg) represents approximately one-tenth the acute oral LD_{50} for males of 0.55 and 0.27 mg/kg, for difethialone and brodifacoum, respectively.

   After the last dose the animals were anesthetized with ether in groups of 5 per test material on successive intervals at 24 hours, 2, 4, 6, 8 and 10 weeks, then at 4, 5 and 6 months for collection of liver tissue. The control group was sacrificed at six months.

   Allocation of test groups for serial sacrifice

	Hour	Week					Month		
	24	2	4	6	8	10	4	5	6
Difethialone	5	5	5	5	5	5	5	5	5
Brodifacoum	5	5	5	5	5	5	5	5	5

   The liver was removed, weighed and a one gram of liver tissue was excised from the main hepatic lobe. Tissue concentrations of the respective test materials were determined by reverse phase High Performance Liquid Chromatography (HPLC) after extraction with acetone. The sensitivity of the analysis allowed "determination of amounts as low as 0.1 ug/g of liver tissue".

HPLC variation coefficient for reproducibility of difethialone and brodifacoum levels in the liver was 7.5 and 7.8%, respectively. The hepatic 1/2 life of each chemical was determined by defining the area under the curve and the elimination constant Ke by calculation from the formula:

$$1/2 = \frac{0.693}{Ke}$$

where the constant Ke represents linearization of the experimental values.

Statistical evaluation involved using either Fisher and Yates T test after estimation of variances, or Mann and Withney's U test.

Results: The mean hepatic levels for the respective test materials are reported in Tables I and II from this report (attached) in ug/g of tissue and ug/organ, respectively.

Hepatic residues of both test materials dropped rapidly as a function of time by day 56 after the last dose (day 77 of the study). During the 77 day to 180 day period, tissue residues leveled off with a slower decrease with time. By the termination of the study at 180 days residues were still detectable by 6.8% and 21.3% of the total dose administered (68 ug/rat) for difethialone and brodifacoum, respectively.

By inspection of Tables I and II the mean liver residue concentrations of brodifacoum were twice that of difethialone between days 22 and 91, followed by a 3-fold difference during the last two months of the study.

The 1/2 life for residues of difethialone and brodifacoum in ug/g of liver are 74 and 136 days, respectively. The 1/2 life for residues of difethialone and brodifacoum in ug/liver are 87 and 144 days, respectively.

Conclusion: The oral administration of 0.06 mg/kg of either difethialone or brodifacoum to 9 groups of 5 animals per group was repeated in four consecutive weekly doses. The test groups were sacrificed in successive intervals after the last dose at 24-hours, then at 2, 4, 6, 8, and 10 weeks followed by 4, 5, and 6 months.

Hepatic residue levels of brodifacoum were eliminated slower than difethialone with a calculated 1/2 life of 140 and 80 days, respectively. After 6 months the hepatic residue concentrations of brodifacoum and difethialone were 21% and 7% of the total dose (68 ug/rat) administered.

This study does not satisfy the Guideline Data Requirement for a General Metabolism Study (85-1), but does satisfy the data request for a modified metabolism study to demonstrate the 1/2 life of difethialone

TABLE I

Hepatic levels in µg/g of tissue after repeated administrations to rats of difethialone or brodifacoum 0.05 mg/kg

Lots	D-22	D-35	D-49	D 63	D-77	D 91	4 months	5 months	6 months
difethialone µg/g ± SD	1.28 ± 0.148	0.76 ± 0.104	0.84 ± 0.148	0.87 ± 0.278	0.49 ± 0.076	0.44 ± 0.102	0.35 ± 0.060	0.29 ± 0.067	0.29 ± 0.070
brodifacoum µg/g ± SD	2.01 ± 0.153	1.81 ± 0.264	1.50 ± 0.475	1.50 ± 0.073	0.98 ± 0.318	0.96 ± 0.113	0.85 ± 0.149	1.09 ± 0.107	0.87 ± 0.162
T and U tests	S^{***}	S^{***}	S^{u}	S^{u}	S^{u}	S^{***}	S^{***}	S^{***}	S^{***}

S^{***}: *significant with p = 0.1%*
Su : significant according to the U test with a level of significance: ≤ 1%

TABLE II

Hepatic concentrations in µg/organ
after 4 administrations to rats
of difethialone or brodifacoum 0.05 mg/kg

Lots	D-22	D-35	D-49	D-63	D-77	D-91	4 months	5 months	6 months
difethialone µg/g ± SD	16.79 ± 2.136	10.03 ± 1.364	13.61 ± 2.746	13.87 ± 3.900	8.63 ± 1.274	7.83 ± 2.014	6.13 ± 1.054	5.11 ± 1.083	4.65 ± 1.409
brodifacoum µg/g ± SD	30.30 ± 3.069	27.45 ± 5.438	25.27 ± 8.462	24.37 ± 2.841	16.19 ± 5.011	16.23 ± 2.106	15.46 ± 3.149	16.00 ± 0.955	14.49 ± 1.989
T and U tests	S^{***}	S^{U}	S^{*}	S^{**}	S^{*}	S^{***}	S^{***}	S^{***}	S^{***}

S^{*}, S^{**}, S^{***}, significant with p = 5, 1 or 0.01% respectively
S^{U}, significant according to the U test with a level of significance, ≤ 1%)